2

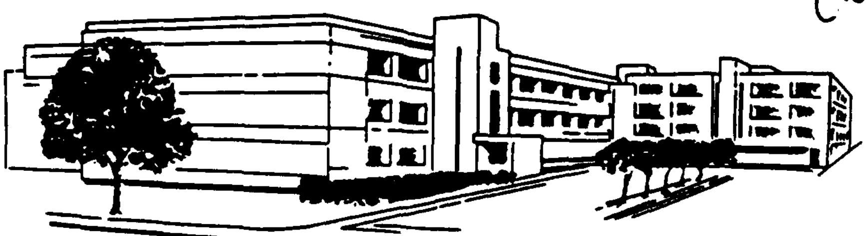
INSTITUTE REPORT NO. 399

Resuscitation With A Bolus Of Hypertonic Saline/Dextran Improves Renal Function Following Hemorrhage in Conscious Swine

J. L Sondeen
G. A. Gonzaludo
J. A. Loveday
W. G. Rodkey
and
C. E. Wade

Division of Military Trauma Research

November 1989



LETTERMAN ARMY INSTITUTE OF RESEARCH PRESIDIO OF SAN FRANCISCO CALIFORNIA 94129

Resuscitation With a Bolus Of Hypertonic Saline/Dextran Improves Renal Function Following Hemorrhage in Conscious Swine, J.L Sondeen et al

The experimental studies of the author described in this report were reviewed and approved by the Institutional Review Committee/Animal Care and Use Committee at Letterman Army Institute of Research. The Manuscript was peer reviewed for compliance prior to submission for publication. In conducting the research described here, the author adhered to the "Guide for the Care and Use of Laboratory Animals," DHEW Publication (NIH) 85-23.

This material has been reviewed by Letterman Army Institute of Research and there is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. (AR 360-5)

Donald G Corby 28 Nov 89

DONALD G. CORBY (date)
COL, MC
Commander

UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT This document has been approved for release and sale. Unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) Institute Report No. 399	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Division of Military Trauma 6b. OFFICE SYMBOL (If applicable) SGRD-ULT-M	7a. NAME OF MONITORING ORGANIZATION U.S. Army Medical Research & Development Command
6c. ADDRESS (City, State, and ZIP Code) Letterman Army Institute of Research Bldg 1110 Presidio of San Francisco, CA 94129	7b. ADDRESS (City, State, and ZIP Code) Ft. Detrick Frederick, MD 21701-5012
8a. NAME OF FUNDING/SPONSORING ORGANIZATION 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code)	10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
HLE0	874	AX	092

11. TITLE (Include Security Classification)

(U) Resuscitation with a bolus of hypertonic saline/dextran improves renal function following hemorrhage in conscious swine.

12. PERSONAL AUTHOR(S)

J Sondeen, G Gonzaludo, J Loveday, W Rodkey, C Wade

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Institute & Journal	FROM ______ TO ______	October 89	24

16. SUPPLEMENTARY NOTATION

Submitted to the Journal Surgery

17. COSATI CODES

FIELD	GROUP	SUB-GROUP

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)

(U) Renal function, HSD, Hemorrhage, Conscious Swine.

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

This study was performed to determine whether resuscitation with a single bolus of 7.5% NaCl/6% Dextran 70 (hypertonic saline/dextran, HSD) could restore renal function following hemorrhage. Chronically instrumented, conscious pigs (n=6) were hemorrhaged 28 ml/kg. Mean arterial pressure (MAP) was reduced from 110 ± 4 to 52 ± 4 mmHg, cardiac output (CO) from 4.2 ± 0.3 to 2.2 ± 0.3 L/min, renal blood flow (RBF) from 238 ± 16 to 57 ± 5 ml/min/kidney, glomerular filtration rate (GFR) from 22 ± 4 to 2 ± 1 ml/min/kidney, and urine flow (V) from 0.70 ± 0.30 to 0.03 ± 0.02 ml/min/kidney. A single, 4 ml/kg bolus injection of HSD increased MAP to 93 ± 7 mmHg, CO to 3.9 ± 0.4 L/min, RBF to 191 ± 20 ml/min/kidney, GFR to 22 ± 6 ml/min/kidney. These improvements were sustained for 2 hours with no further treatment. Urine flow transiently increased to 0.40 ± 0.20 ml/min/kidney, but then subsided to 0.20 ± 0.02 ml/min/kidney at 60 min. Plasma osmolality increased from 275 ± 4 to 282 ± 5 mOsm/kg H_2O, and plasma sodium increased from 141 ± 3 to 149 ± 5 mEq/L. Recovery following administration of an equal volume of normal saline

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL Jill L. Sondeen	22b. TELEPHONE (Include Area Code) 561-5816 · 22c. OFFICE SYMBOL SGRD-ULT-M

DD Form 1473, JUN 86 — Previous editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE

UNCLASSIFIED

ABSTRACT (Con't)

(n=5) was significantly less. Euvolemic animals (n=5) showed no response in MAP, CO, RBF, or GFR when treated with HSD although V, osmotic and sodium excretion increased. These results demonstrate that resuscitation with HSD following hemorrhage not only restores MAP and CO but maintains renal function as well.

ABSTRACT

This study was performed to determine whether resuscitation with a single bolus of 7.5% NaCl/6% Dextran 70 (hypertonic saline/dextran, HSD) could restore renal function following hemorrhage. Chronically instrumented, conscious pigs (n=6) were hemorrhaged 28 ml/kg. Mean arterial pressure (MAP) was reduced from 110 $\pm$ 4 to 52 $\pm$ 4 mmHg, cardiac output (CO) from 4.2 $\pm$ 0.3 to 2.2 $\pm$ 0.3 L/min, renal blood flow (RBF) from 238 $\pm$ 16 to 57 $\pm$ 5 ml/min/ kidney, glomerular filtration rate (GFR) from 22 $\pm$ 4 to 2 $\pm$ 1 ml/min/kidney, and urine flow (V) from 0.70 $\pm$ 0.30 to 0.03 $\pm$ 0.02 ml/min/kidney. A single, 4 ml/kg bolus injection of HSD increased MAP to 93 $\pm$ 7 mmHg, CO to 3.9 $\pm$ 0.4 L/min, RBF to 191 $\pm$ 20 ml/min/kidney, GFR to 22 $\pm$ 6 ml/min/kidney. These improvements were sustained for 2 hours with no further treatment. Urine flow transiently increased to 0.40 $\pm$ 0.20 ml/min/kidney, but then subsided to 0.20 $\pm$ 0.02 ml/min/kidney at 60 min. Plasma osmolality increased from 275 $\pm$ 4 to 282 $\pm$ 5 mOsm/kg H_2O, and plasma sodium increased from 141 $\pm$ 3 to 149 $\pm$ 5 mEq/L. Recovery following administration of an equal volume of normal saline (n=5) was significantly less. Euvolemic animals (n=5) showed no response in MAP, CO, RBF, or GFR when treated with HSD although V, osmotic and sodium excretion increased. These results demonstrate that resuscitation with HSD following hemorrhage not only restores MAP and CO but maintains renal function as well.

Resuscitation with a bolus of hypertonic saline/dextran improves renal function following hemorrhage in conscious swine -- Sondeen et al.

INTRODUCTION

The mortality rate from severe trauma has decreased dramatically since the importance of immediate treatment has been recognized and implemented(1). However, controversy has arisen whether rapid transport should be emphasized rather than attempts at pre-hospital stabilization of patients: the small amount of isotonic fluid that can be infused during the average 20-minute travel time is thought to have minimal therapeutic effect and the delay may render definitive treatment ineffective (2,3).

As first shown in the anesthetized dog in 1980, (4) and later corroborated in many other species including conscious sheep (5,6) and pigs, (7,8) a bolus of a small volume (~4 ml/kg) of a hypertonic hyperoncotic solution (7.5% NaCl with 6% Dextran 70, HSD) improves arterial pressure, cardiac output, and survival rates following hemorrhagic shock (4-8). The efficacy of HSD for resuscitation of humans following surgery or severe trauma is currently being tested in clinical trials (9-11). The volume of fluid injected, about 200 ml, is small enough to be administered easily during transport (2), and the beneficial effects begin even before the injection of HSD is completed (12). Thus, use of HSD in the field may improve the cardiodynamic status of the patient before definitive treatment is available.

In a rural or battlefield situation where immediate transport is not readily available, the beneficial effects of HSD may be even more important. Prolonged shock will inevitably result in organ failure (13-15) and even if hypovolemia is successfully treated, acute renal failure can ensue several days later. The mortality rate associated with acute renal failure remains quite high (15). Therefore, we conducted the present study to determine whether the administration of a bolus of HSD following hemorrhage would restore renal blood flow and function and maintain it for 2 hours, an interval chosen to simulate the maximum time it may take for the patients to obtain definitive care.

METHODS

Surgical preparation. Twenty-one, immature female Yorkshire/Duroc swine (J. G. Boswell, Concoran, CA) weighing 20-25 kg were used. The animals were fasted 24 hours before surgery with water available ad lib. On the morning of surgery, the pigs were premedicated with ketamine HCl (2.2 mg/kg), xylazine HCl (2.2 mg/kg), and atropine (0.1 mg/kg), anesthetized with halothane using a snout mask, intubated and maintained on a mixture of 1% halothane, delivered in N_2O and O_2 on a ventilator. All surgery was performed using aseptic techniques.

The spleen was removed via a midline laparotomy. A catheter was inserted into the splenic vein with its tip advanced into the portal vein. Then, the left kidney was approached through the same midline incision. The ureter was non-occlusively catheterized through a hole in the ventral wall of the ureter near its junction with the renal pelvis. A 10-French pediatric Malecot catheter was passed through the hole toward the kidney and secured with a purse-string suture. A snare of PE-160 tubing was placed around the ureter approximately 2 cm distal to the Malecot catheter. The ends of the tubing were threaded through a PE-350 sleeve. An ultrasonic flow probe (6 mm, Transonic Systems, Inc.) was placed around the renal artery for measuring renal blood flow. The cable of the flow probe and distal ends of the catheters were coiled in the retroperitoneal space adjacent to the kidney. The peritoneum was closed and the laparotomy incision was sutured in layers.

The pig was repositioned onto its right side and a left flank incision was made. A large bore polyvinyl catheter (0.125 inch, i.d.) was implanted non-occlusively in the infrarenal aorta for blood withdrawal and blood pressure monitoring. The Malecot, vascular catheters, and flow probe cable were exteriorized to the back and protected with a Velcro patch. Through a midline incision in the neck, a 5-French pediatric Swan-Ganz catheter was inserted into the pulmonary artery via the left jugular vein. This catheter was used for cardiac output determinations using the thermodilution method. The end of the catheter was exteriorized to the back and protected with a Velcro patch. The catheters were flushed and subsequently filled with heparin (1000 U/ml) daily to maintain patency. Keflin (1 g/day) was administered on the day of and for three days following surgery to prevent infection. The animal was allowed to recover 7 to 10 days following surgery before the experiment was performed.

Experimental Protocol. The pig was fasted 18 h prior to the experiment with water available ad lib. On the day of the experiment, the pig was placed in a modified Pavlov sling. An extension tube was connected to the ureteral catheter, the snare was tightened to occlude urine flow distally and urine was allowed to flow freely into a graduated cylinder. The arterial catheter, Swan-Ganz catheter and flow probe were connected to a P23Db pressure transducer (Statham Gould) and polygraph (Gould), a cardiac output computer (Gould), and an ultrasonic blood flow meter (Transonic), respectively.

Sixty minutes were allowed for the animal to become accustomed to the surroundings before measuring pre-hemorrhage creatinine, electrolyte and osmotic clearance rates. A clearance measurement consisted of a timed urine collection (20 min) with an arterial blood sample (12 ml) taken at the midpoint. Following this baseline period, 28 ml/kg blood was removed continuously over 44 min in such a fashion to imitate a hemorrhage from a severed artery. To achieve this, blood was removed in 7 ml/kg increments, i.e., 7 ml/kg over 9 min, over 10 min, over 12 min, and over 13 min. A 12-ml aliquot of the shed blood was collected at the end of the bleed period or a 12-ml sample was collected at the same time period in the time control experiments. At the end of the hemorrhage, and at 15 min, 60 min, and 120 min following treatment, blood pressure, cardiac output, renal blood flow, and urine flow rate were measured. Treatment with a 4 ml/kg bolus of either 0.9% NaCl (normal saline, NS) or 7.5% NaCl/6% Dextran 70 (HSD) followed the first set of measurements. There were 4 groups: 1) non-hemorrhaged control with NS, n=5; 2) non-hemorrhaged control with HSD, n=5; 3) 28 ml/kg hemorrhage with NS, n=5; 4) 28 ml/kg hemorrhage with HSD, n=6.

After the experiment, the animals were euthanized with an overdose of barbiturate. A gross necropsy examination was performed to assess catheter placement and to ensure no abnormalities were present.

Sample analyses. The blood samples were heparinized and plasma was removed following centrifugation. Concentrations of sodium, potassium, and creatinine in the plasma and urine samples were measured using an autoanalyzer (Roche Analytical Instruments, COBAS FARA Model) with ion specific electrodes for sodium and potassium and a modified Jaffe reaction method for creatinine. Plasma and urine osmolalities were measured with a freezing-point depression osmometer (Advanced III). Hematocrit was measured in duplicate by the microcapillary method (IEC MB Centrifuge).

Calculations. Clearances were calculated for creatinine, sodium, potassium, and osmolality using the following formula: $\text{Clearance}_x = (U_x \times V)/P_x$, where U_x is the urine concentration of substance x, V is the urine flow rate (ml/min), and P_x is the plasma concentration of x. Free water clearance was calculated by subtracting osmotic clearance from urine flow rate. Creatinine clearance was used to estimate glomerular filtration rate (GFR). Fractional excretion was calculated by dividing the clearance of sodium or potassium by GFR. Renal plasma flow (RPF) was estimated by dividing the RBF measured with the flow probe by the calculated plasma fraction [(100-hematocrit)/100]. Filtration fraction was calculated by dividing the GFR by the RPF.

Statistical analysis. A one-way analysis of variance was used to determine whether baseline values were homogeneous among the four groups (16). To ascertain whether changes occurred with time, a one-way analysis of variance with repeated measures was performed for each group (16). To ascertain whether there was any difference between the treatments with NS and HSD, a two-way analysis of covariance was performed with repeated measures on the time factor and non-repeated measures between the treatment groups (16). The value at the end of hemorrhage or the appropriate time in the euvolemic experiments was used as the covariate. The data in the graphs have been adjusted for the corresponding (euvolemic or hypovolemic) covariate. If there was a significant ($P \leq 0.05$) difference between the factors, a Newman-Keuls multiple range test was performed on the means to locate the difference (17). The data are presented as means ±SEM. In several cases, not all measurements were made in each animal due to catheter or flow probe failure. The number of animals included for each of the data analyses are shown on the tables.

RESULTS

Responses to hemorrhage. The 28 ml/kg hemorrhage decreased mean arterial pressure (MAP) and cardiac output (CO) by 53% and 44%, respectively (Table I). There was no increase in total peripheral resistance (TPR) immediately following hemorrhage (Table I). Renal blood flow was reduced by 77% and GFR by 83%, while renal vascular resistance (RVR) almost doubled (186%) in response to the 28 ml/kg hemorrhage (Table I).

The urine flow rate, osmotic and free-water clearance, and electrolyte excretion responses to the hemorrhage are shown in Table II. Although there were strong trends indicating reduced urinary excretory functions in response to the hemorrhage, in many cases they did not reach statistical significance. However, when animals were combined into non-hemorrhagic and hemorrhagic groups, significant reductions in response to hemorrhage were detected. Urine flow rate (V) decreased by 90%, from 0.76 ± 0.25 to 0.08 ± 0.04 ml/min/kidney ($P<0.05$) and osmotic clearance (C_{Osm}) decreased by 86%, from 0.43 ± 0.06 to 0.06 ± 0.05 ml/min/kidney ($P<0.05$). There was no significant effect on free-water clearance (C_{H2O}). Hemorrhage induced an 85% decrease in Na excretion ($U_{Na}V$), from 26 ± 8 to 4 ± 3 μEq/min/kidney ($P<0.05$), and a 40% decrease in K excretion (U_KV), from 10 ± 2 to 6 ± 1 μEq/min/kidney ($P<0.001$). Although part of the decrease in electrolyte excretion may have been due to the decrease in GFR, even after accounting for changes in GFR, a significant (77%) decrease in the fractional excretion of Na (FE_{Na}) remained, from 0.88 ± 0.26 to 0.20 ± 0.09% ($P<0.05$). The 45% decrease in fractional excretion of K (FE_K), from 9.4 ± 2.9 to 5.2 ± 2.8%, did not reach statistical significance.

Plasma osmolality (P_{Osm}) showed a tendency to rise in response to hemorrhage, with 8 out of 11 animals increasing their P_{Osm} following hemorrhage. The P_{Osm} response to hemorrhage was significant in the NS group (Table III). The change in P_{Osm} was not due to changes in plasma electrolytes because there were no significant changes in plasma sodium (P_{Na}). Plasma potassium (P_K) showed a slight tendency to decrease, although not significantly. This degree of hemorrhage caused plasma dilution to reduce hematocrit (Hct) by 23% (Table III).

No significant changes occurred during the first 44 min of the non-hemorrhage control experiments in any of the variables measured (Tables I and II), except for P_K which showed a significant decrease in the HSD control group (Table III).

Responses to resuscitation treatment. During the first 15 min following the injection of 4 ml/kg of NS, the hemorrhaged animals showed a rapid MAP increase of 26 mmHg, from 46% of the non-hemorrhaged value to 70%; pressure gradually continued to increase, reaching 76% of non-hemorrhaged value at 120 min (Fig. 1). HSD caused a significantly greater response than NS, increasing MAP by 43 mmHg to reach a level 83% of the non-hemorrhaged value (Fig. 1).

Despite the effect NS had on MAP in the hemorrhaged animal, NS treatment did not affect CO (Fig. 1). In contrast, administering HSD caused a dramatic increase in CO from a nadir of 54%, reaching 74% of the non-hemorrhaged value at 15 min, gradually increasing to a value not significantly different from the non-hemorrhaged control at 60 min (Fig. 1). TPR was significantly lower (31%) in the HSD-treated animals than in the NS-treated animals after 60 min (Fig. 1). Treating euvolemic pigs with either NS or HSD had no significant effect on MAP, CO, or TPR (Fig. 1).

In the hemorrhaged animals, RBF increased from a nadir of 21% to 36% of the non-hemorrhaged control in response to the NS treatment (Fig. 2). HSD enhanced this recovery so that RBF reached 61% of the non-hemorrhaged value, but RBF was still significantly below control levels. The RVR was elevated in the hemorrhaged animals and remained significantly elevated in the NS-treated group (Fig. 2). In contrast, treatment with HSD returned RVR to non-hemorrhaged control levels within 15 min. Although HSD treatment tended to increase GFR, reaching 88% of the non-hemorrhaged control after 15 min, the response was not statistically significant. Following treatment with NS, GFR was 3% of the non-hemorrhaged control at 15 min, but then tended to increase over the next 2 hours such that, by 60 min, it was not significantly different from non-hemorrhaged values (Fig. 2). When given to euvolemic pigs, treatment with either NS or HSD had no significant effect on RBF, RVR, or GFR (Fig. 2).

The urinary excretory responses are shown in Figures 3 and 4. Urine flow rate did not change following NS treatment in hemorrhaged animals (Fig. 3). Treatment with HSD, however, caused a transient, 0.33 ml/min/kidney increase in urine flow rate in the hemorrhaged animals. In euvolemic animals, NS had no significant effect on V, but HSD caused a transient, 0.59 ml/min/kidney increase. A total urine volume of 160 ± 84 ml was excreted over the entire experimental period (189 min) by the euvolemic, HSD-treated animals compared with 32 ± 9 ml excreted by the hypovolemic, HSD-treated animals ($P<0.01$). For comparison, a total urine volume of 116 ± 76 ml was excreted by the euvolemic, NS-treated animals compared to 15 ± 5 ml excreted by the hypovolemic, NS-treated animals ($P<0.05$). The volume excreted by the hemorrhaged animals treated with HSD was significantly ($P<0.01$) greater than that excreted by the NS-treated, hemorrhaged animals.

The changes in C_{Osm} were analogous to changes in urine flow rate (Fig. 3). Thus, C_{Osm} was increased in response to HSD-treatment in either euvolemic (+2.2 ± 0.1 ml/min/kidney at 15 min) or hypovolemic (+2.8 ± 0.2 ml/min/kidney at 15 min) pigs but not in response to NS-treatment. There was no significant change in C_{H2O} in response to any of the treatments in either euvolemia or hypovolemia (Fig. 3). The increase in osmotic excretion in response to HSD was almost entirely due to an increase in $U_{Na}V$ (Fig. 4). There was no significant increase in U_KV in response to HSD in the hemorrhaged animals (Fig. 4, note scale). Hypovolemia significantly inhibited the natriuretic response caused by treatment with HSD. $U_{Na}V$ thus increased by 420 ± 19 µEq/min/kidney in the euvolemic animals at 15 min but only by 282 ± 20 µEq/min/kidney in the hypovolemic animals. When corrections for changes in GFR were made, the pattern of changes in FE_{Na} and FE_K were similar to those shown for $U_{Na}V$ and U_KV, but the changes did not reach statistical significance (data not shown).

Despite large differences in the urinary excretion of sodium, there were almost identical changes in P_{Na} in response to HSD treatment in both euvolemic and hypovolemic animals (Fig. 5). In euvolemic animals, there was a significant reduction in P_K in response to HSD at 15 min and a tendency for P_K to decrease in response to NS (Fig. 5). In hypovolemic animals, treatment with either NS or HSD caused very similar and significant decreases in P_K (Fig. 5) at 15 min. The hematocrit was significantly lower in the hemorrhaged animals compared to the euvolemic animals, but there were no significant differences between NS and HSD treatments in the hypovolemic animals (Fig. 5).

DISCUSSION

This study provides evidence that not only does a single, 4 ml/kg bolus of HSD improve MAP and CO in response to hemorrhage (Fig. 1), but it also preserves kidney function. In the present experiment, HSD increased RBF to 61% and GFR to 88% of the non-hemorrhaged control values. These increases were sustained for the full 2 hours of observation with no further treatment (Fig. 2).

These results confirm earlier studies showing RBF increases in response to resuscitation with a bolus of HSD following hemorrhage, although RBF does not completely return to baseline values (8) (Fig. 2). Other studies using infusions of larger volumes of less concentrated hypertonic saline have also shown that GFR is restored (18,19). However, the present study is the first study to demonstrate that a single injection of a small volume of HSD can restore and maintain GFR (Fig. 2).

Treatment with HSD produced transient increases in urine flow and electrolyte/osmotic excretion (Fig. 2 and 3) but the rates were not so excessive that they would lead to dehydration: a total volume of 32 ml/kidney or an estimated 0.2% of total body water (~1.2% of extra-cellular water) was excreted over 2 hours. The magnitude of the peak urine flow in hypovolemic pigs in response to a bolus of HSD was less than that observed in hypovolemic sheep (6). Differences in the magnitude of the response may be due to species dissimilarities or to experimental protocol; the sheep were maintained at 50 mmHg for 3 hours compared with about 20 min for the pigs used in the present study. In other experiments measuring the renal excretory function in response to an infusion of hypertonic saline of lower concentration (1.8%) and administering NS until a specific physiological effect was achieved (restoration of central venous pressure), neither pigs (18) nor humans (19-21) responded with an excessive diuresis which would exacerbate hypovolemia.

Although it is well-known that infusions of hypertonic salt solutions induce a diuresis and a natriuresis - this occurred in both the control as well as the hemorrhage experiments (Figures 3 and 4) - the urine flow and osmotic/electrolyte excretion rates were significantly reduced during hemorrhage. Hemorrhage causes increases in vasopressin, aldosterone, angiotensin II, and the catecholamines, all known to decrease water and sodium excretion (22). HSD treatment causes these hormones to return toward baseline levels (6). The reduction in renal vascular resistance and the increase in sodium excretion could be due to the decrements in these neurohumoral substances. Part of the increase in osmotic clearance observed following HSD treatment could also be due to an increase in urinary dextran. Dubick et al. (23) showed that urinary excretion of dextrans with molecular weight greater than 50,000 was increased following hemorrhage after treatment with HSD.

The use of hypertonic solutions has been shown effective for the treatment of hypovolemia resulting from burns (24), hemorrhage (4-8,12,18), trauma (9,10), and surgery (19-21). To achieve comparable improvements in arterial or central venous pressure, solutions with concentrations of 1.8%, 3%, and 7.5% NaCl or 6% Dextran 70 have universally required less volume for resuscitation when compared to the traditional isotonic lactated Ringer's solution (6,18-21,25,26). Other advantages associated with the use of hypertonic solutions include decreases in intracranial pressure and cerebral edema (18,25-27), a decrease in the drainage volume of chest fluid following heart surgery (21), faster restoration of intestinal function (19), and less edema (18,28,29). HSD is thought to have its beneficial cardiovascular effects by a direct inotropic effect on the heart, dilation of the veins and arteries to increase venous return, and increase in plasma volume by transfer from the intracellular to the intravascular fluid compartment (12). Hypertonicity may directly stimulate pulmonary receptors to elicit a neural reflex, possibly explaining the dramatic effects on MAP which occur even before significant changes in plasma volume (30). Hypertonic solutions also may decrease vascular resistance and improve intestinal function by a direct effect to decrease endothelial cell swelling (28).

In conclusion, in situations with logistical constraints that limit the transport and use of large amounts of intravenous fluids, or with unavoidable delays in transport to a definitive treatment facility, the small volume of HSD may provide an important tool in effectively treating hemorrhage and trauma victims. In both human and animal studies, no adverse effects have been observed from administering the small volume dose of HSD (6-11, 23). However, the present and previous studies have shown that a single bolus of HSD can dramatically improve blood pressure, cardiac output and restore and maintain renal function following hemorrhage and trauma.

ACKNOWLEDGMENTS

The authors express their appreciation for the technical assistance of Gary Bonner and Edward Potanko.

REFERENCES

1. Trunkey DD. Overview of trauma. Surg Clin North Am 1982;62:3-7.

2. Smith JP, Bodai BI, Hill AS, Frey CF. Prehospital stabilization of critically injured patients: a failed concept. J Trauma 1985;25:65-70.

3. Chudnofsky CR, Dronen SC, Syverud SA, Hedges JR, Zink BJ. Early versus late fluid resuscitation: lack of effect in porcine hemorrhagic shock. Ann Emerg Med 1989;18:122-126.

4. Velasco IT, Pontieri V, Rocha e Silva M, Lopes OU. Hyperosmotic NaCl and severe hemorrhagic shock. Am J Physiol 1980;239:H664-H673.

5. Smith GJ, Kramer GC, Perron P, Nakayama S-I, Gunther RA, Holcroft JW. A comparison of several hypertonic solutions for resuscitation of bled sheep. J Surg Res 1985;39:517-528.

6. Kramer GC, Perron PR, Lindsey C, et al. Small-volume resuscitation with hypertonic saline dextran solution. Surgery 1986;100:239-246.

7. Maningas PA, DeGuzman LR, Tillman FJ, Hinson CS, Priegnitz KJ, Volk KA. Small-volume infusion of 7.5% NaCl in 6% Dextran-70 for the treatment of severe hemorrhagic shock in swine. Ann Emerg Med 1986;15:1131-1137.

8. Maningas PA. Resuscitation with 7.5% NaCl in 6% Dextran-70 during hemorrhagic shock in swine: effects on organ blood flow. Crit Care Med 1987;87:1121-1126.

9. Holcroft JW, Vassar MJ, Turner JE, Derlet RW, Kramer GC. 3% NaCl and 7.5% NaCl/Dextran-70 in the resuscitation of severely injured patients. Ann Surg 1987;206:279-288.

10. Holcroft JW, Vassar MJ, Perry CA, Gannaway WL, Kramer GC. Perspectives on clinical trials for hypertonic saline/dextran solutions for the treatment of traumatic shock. Braz J Med Biol Res 1989;22:291-293.

11. Maningas PA, Mattox KL, Pepe PE, Jones RL, Feliciano DV, Burch JM. Hypertonic saline-dextran solutions for the prehospital management of traumatic hypotension. Am J Surg 1989;157:528-533.

12. Kramer GC, English TP, Gunther RA, Holcroft JW. Physiological mechanisms of fluid resuscitation with hyperosmotic/hyperoncotic solutions. In: Passmore JC, ed. Perspectives in shock research: metabolism, immunology, mediators, and models. New York: Alan R. Liss, Inc. 1989:311-320.

13. Passmore JC. Role of the kidney in shock: current views. In: Altura BM, et al., ed. Handbook of shock and trauma. vol. 1: Basic science. New York: Raven Press,1983:113-128.

14. Lucas CE, Ledgerwood A. Renal response to hypovolaemic shock. In: Shires GT, ed. Shock and related problems, Clinical surgery international. vol 9. Edinburgh:Churchill Livingstone,1984,81-94.

15. Sirinek KR, Hura CE. Renal failure. In: Mattox KL, et al., ed. Trauma. Norwalk, CT: Appleton and Lange,1988:835-848.

16. Winer BJ. Statistical Principles in Experimental Design. New York: McGraw-Hill Book Co., 1971.

17. Zar JH. Biostatistical Analysis. New Jersey: Prentice-Hall, Inc., 1974.

18. Shackford SR, Norton CH, Todd MM. Renal, cerebral, and pulmonary effects of hypertonic resuscitation in a porcine model of hemorrhagic shock. Surgery 1988;104:553-560.

19. Shackford SR, Sise MJ, Fridlund PH, et al. Hypertonic sodium lactate versus lactated Ringer's solution for intravenous fluid therapy in operations on the abdominal aorta. Surgery 1983;94:41-51.

20. Shackford SR, Fortlage DA, Peters RM, Hollinsworth-Fridlund P, Sise MJ. Serum osmolar and electrolyte changes associated with large infusions of hypertonic sodium lactate for intravascular volume expansion of patients

undergoing aortic reconstruction. Surg Gynecol Obstet 1987;164:127-136.

21. Cross JS, Gruber DP, Burchard KW, Singh AK, Moran JM, Gann DS. Hypertonic saline fluid therapy following surgery: a prospective study. J Trauma 1989;29:817-826.

22. Carlson, DE, DeMaria EJ, Campbell, RW, and Gann, DS. Behavioral and hormonal influence on blood volume restitution after hemorrhage in swine. Am J Physiol 1989;256:R207-R216.

23. Dubick MA, Summary JJ, Ryan BA, Wade CE. Dextran concentrations in plasma and urine following administration of 6% Dextran-70/7.5% NaCl to hemorrhaged and euvolemic conscious swine. Circ Shock;In press.

24. Monafo WW, Halverson JD, Schechtman K. The role of concentrated sodium solutions in the resuscitation of patients with severe burns. Surgery 1984;95:129-135.

25. Todd MM, Tommasino C, Moore S. Cerebral effects of isovolemic hemodilution with a hypertonic saline solution. J Neurosurg 1985;63:944-948.

26. Zornow MH, Scheller MS, Shackford SR. Effect of a hypertonic lactated Ringer's solution on intracranial pressure and cerebral water content in a model of traumatic brain injury. J Trauma 1989;29:484-488.

27. Gunnar WP, Merlotti GJ, Jonasson O, Barrett J. Resuscitation from hemorrhagic shock: alterations of the intracranial pressure after normal saline, 3% saline, and Dextran-40. Ann Surg 1986;204:686-692.

28. Nakayama S-I, Kramer GC, Carlsen RC, Holcroft JW. Infusion of very hypertonic saline to bled rats: membrane potentials and fluid shifts. J Surg Res 1985;38:180-186.

29. Linko K, Mäkeläinen A. Hydroxyethyl starch 120, Dextran-70 and acetated Ringer's solution: hemodilution, albumin, colloid osmotic pressure

and fluid balance following replacement of blood loss in pigs. Acta Anaesthesiol Scand 1988;32:228-233.

30. Younes RN, Aun F, Tomida RM, Birolini D. The role of lung innervation in the hemodynamic response to hypertonic sodium chloride solutions in hemorrhagic shock. Surgery 1985;98:900-906.

TABLE I. Systemic and renal hemodynamic responses to hemorrhage.

GROUP		N	BASELINE	PRE-TREATMENT
			Mean Arterial Pressure (mmHg)	
Non-hemorrhage	NS	5	110 ± 3	111 ± 2
	HSD	4	113 ± 5	112 ± 6
Hemorrhage	NS	5	111 ± 4	53 ± 3*+
	HSD	6	110 ± 4	52 ± 4*+
			Cardiac Output (L/min)	
Non-hemorrhage	NS	5	5.5 ± 0.8	4.5 ± 0.6
	HSD	5	4.3 ± 0.1	4.8 ± 0.5
Hemorrhage	NS	5	4.6 ± 0.4	2.9 ± 0.3*
	HSD	6	4.2 ± 0.3	2.2 ± 0.3*+
			Total Peripheral Resistance (PRU)	
Non-hemorrhage	NS	5	22 ± 4	27 ± 3
	HSD	4	27 ± 1	25 ± 5
Hemorrhage	NS	5	25 ± 2	20 ± 4*
	HSD	6	27 ± 2	26 ± 4
			Renal Blood Flow (ml/min/kidney)	
Non-hemorrhage	NS	5	269 ± 54	289 ± 54
	HSD	5	256 ± 41	257 ± 47
Hemorrhage	NS	4	213 ± 24+	59 ± 13*+
	HSD	5	238 ± 16	57 ± 5*+
			Renal Vascular Resistance (PRU/kidney)	
Non-hemorrhage	NS	5	0.48 ± 0.09	0.45 ± 0.08
	HSD	4	0.52 ± 0.20	0.54 ± 0.11
Hemorrhage	NS	4	0.57 ± 0.09	1.00 ± 0.19*+
	HSD	5	0.47 ± 0.02	0.89 ± 0.08*+
			Glomerular Filtration Rate (ml/min/kidney)	
Non-hemorrhage	NS	5	29 ± 5	26 ± 4
	HSD	5	24 ± 3	30 ± 6
Hemorrhage	NS	5	28 ± 5	7 ± 6*+
	HSD	6	22 ± 4	2 ± 1*+

*P<0.05 different from pre-hemorrhage baseline value.

+P<0.05 different from same time point in non-hemorrhage control experiment.

The data for the normal saline (NS) and hypertonic saline/dextran (HSD) groups is arranged according to the treatment the animals will receive immediately following the pre-treatment measurement.

TABLE II. Urinary excretory responses to hemorrhage.

GROUP		N	BASELINE	PRE-TREATMENT
			Urine Flow Rate (ml/min/kidney)	
Non-hemorrhage	NS	5	0.68 ± 0.18	0.98 ± 0.49
	HSD	5	0.65 ± 0.17	0.85 ± 0.34
Hemorrhage	NS	5	0.87 ± 0.42	0.13 ± 0.08
	HSD	6	0.67 ± 0.29	0.03 ± 0.02+
			Osmotic Clearance (ml/min/kidney)	
Non-hemorrhage	NS	5	0.33 ± 0.08	0.46 ± 0.21
	HSD	5	0.53 ± 0.10	0.79 ± 0.24
Hemorrhage	NS	4	0.39 ± 0.05	0.16 ± 0.13
	HSD	6	0.45 ± 0.10	0.00 ± 0.00*+
			Free-water Clearance (ml/min/kidney)	
Non-hemorrhage	NS	5	0.35 ± 0.12	0.52 ± 0.30
	HSD	5	0.12 ± 0.14	0.06 ± 0.12
Hemorrhage	NS	4	0.01 ± 0.04	-0.01 ± 0.02
	HSD	6	0.21 ± 0.22	0.02 ± 0.01
			Sodium Excretion Rate (µEq/min/kidney)	
Non-hemorrhage	NS	5	24 ± 8	42 ± 25
	HSD	5	29 ± 12	38 ± 21
Hemorrhage	NS	4	23 ± 6	8 ± 7+
	HSD	6	28 ± 13	1 ± 1
			Potassium Excretion Rate (µEq/min/kidney)	
Non-hemorrhage	NS	5	11.0 ± 5.0	14.4 ± 4.6
	HSD	5	21.5 ± 6.6	26.0 ± 9.3
Hemorrhage	NS	4	12.2 ± 4.9	2.2 ± 1.3
	HSD	6	8.8 ± 2.3	0.6 ± 0.4+
			Fractional Excretion of Sodium (%/kidney)	
Non-hemorrhage	NS	5	0.65 ± 0.21	1.00 ± 0.41
	HSD	5	0.89 ± 0.40	0.97 ± 0.45
Hemorrhage	NS	4	0.67 ± 0.13	0.30 ± 0.18
	HSD	6	1.02 ± 0.43	0.14 ± 0.11
			Fractional Excretion of Potassium (%/kidney)	
Non-hemorrhage	NS	5	7.7 ± 2.9	12.4 ± 3.3
	HSD	5	18.6 ± 5.3	16.4 ± 3.0
Hemorrhage	NS	4	12.0 ± 5.6	7.0 ± 5.8
	HSD	6	7.7 ± 3.2	4.0 ± 3.0+

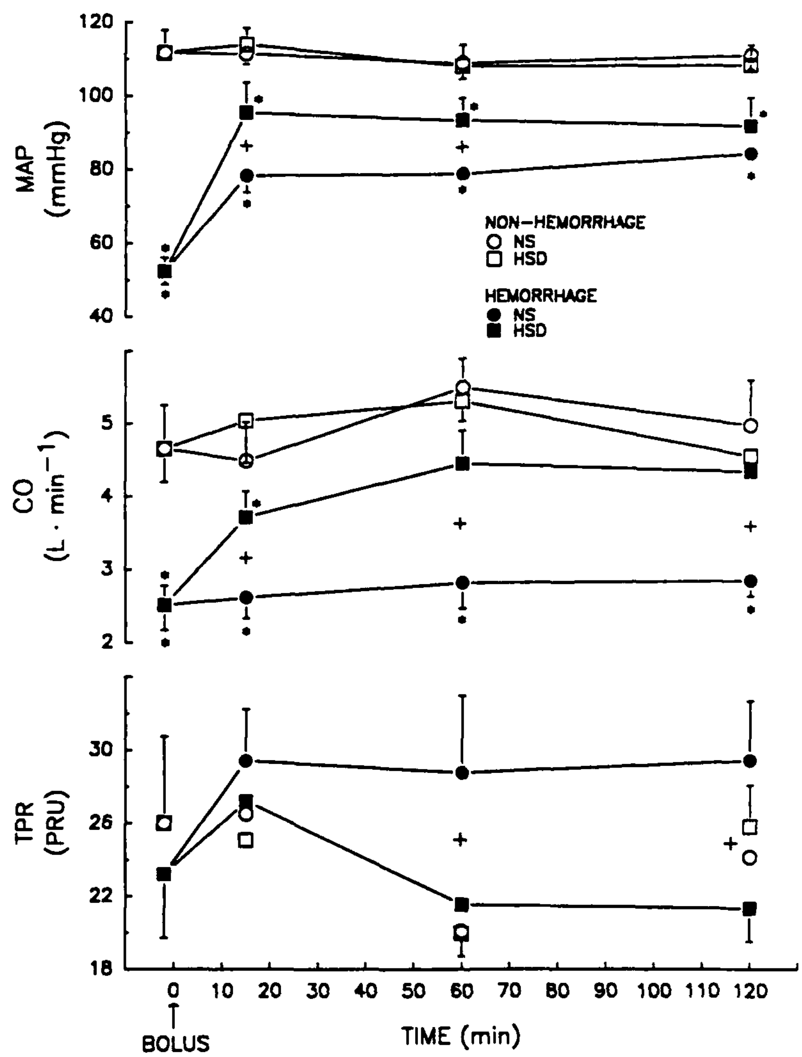
See Table I for key.

TABLE III. Plasma osmolality, plasma electrolyte, and hematocrit responses to hemorrhage.

GROUP		N	BASELINE	PRE-TREATMENT
			Plasma Osmolality (mOsm/kg H2O)	
Non-hemorrhage	NS	5	274 ± 4	276 ± 4
	HSD	5	279 ± 8	278 ± 6
Hemorrhage	NS	5	282 ± 2+	288 ± 2*+
	HSD	6	273 ± 4	275 ± 4
			Plasma Sodium (mEq/L)	
Non-hemorrhage	NS	5	139.9 ± 4.4	139.4 ± 4.5
	HSD	5	138.9 ± 3.6	140.3 ± 4.0
Hemorrhage	NS	5	139.1 ± 3.2	140.4 ± 3.5
	HSD	6	139.7 ± 2.2	140.8 ± 2.8
			Plasma Potassium (mEq/L)	
Non-hemorrhage	NS	5	4.64 ± 0.49	4.66 ± 0.39
	HSD	5	5.12 ± 0.31	4.70 ± 0.24*
Hemorrhage	NS	5	4.62 ± 0.14	4.48 ± 0.09
	HSD	6	4.87 ± 0.21	4.57 ± 0.22
			Hematocrit (%RBC)	
Non-hemorrhage	NS	5	29 ± 1	28 ± 2
	HSD	5	30 ± 2	29 ± 2
Hemorrhage	NS	5	31 ± 1+	25 ± 1*+
	HSD	6	30 ± 1	22 ± 2*+

See Table 1 for key.

FIGURE LEGENDS



+ P < 0.05 difference between NS and HSD treatment.

* P < 0.05 difference between hemorrhage and non-hemorrhaged control value at the same time point.

Figure 1: Mean arterial pressure (MAP), cardiac output (CO), and total peripheral resistance (TPR) in response to a 4 ml/kg bolus of normal saline (NS) or hypertonic saline/dextran (HSD). The immediately-post-hemorrhage value or the corresponding non-hemorrhaged control value was averaged over the NS and HSD groups. Selected error bars have been omitted for clarity.

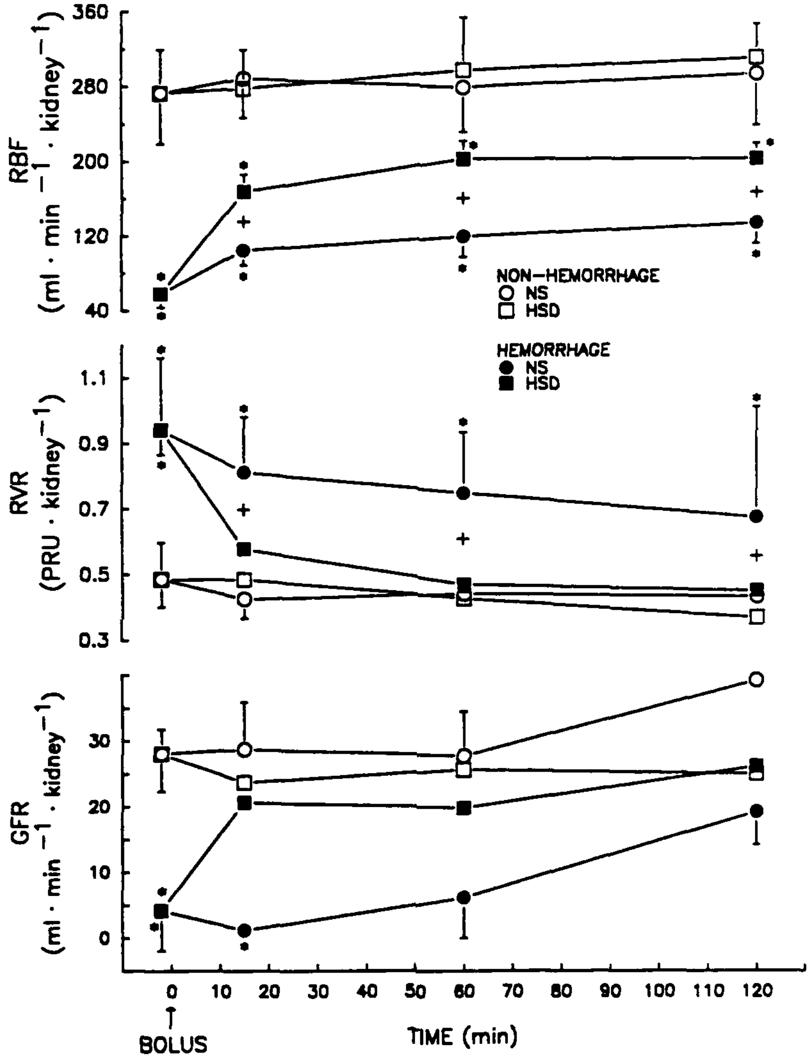


Figure 2: Renal blood flow (RBF), renal vascular resistance (RVR), and glomerular flow rate (GFR) in response to a 4 ml/kg bolus of normal saline (NS) or hypertonic saline/dextran (HSD). See legend in Figure 1 for details.

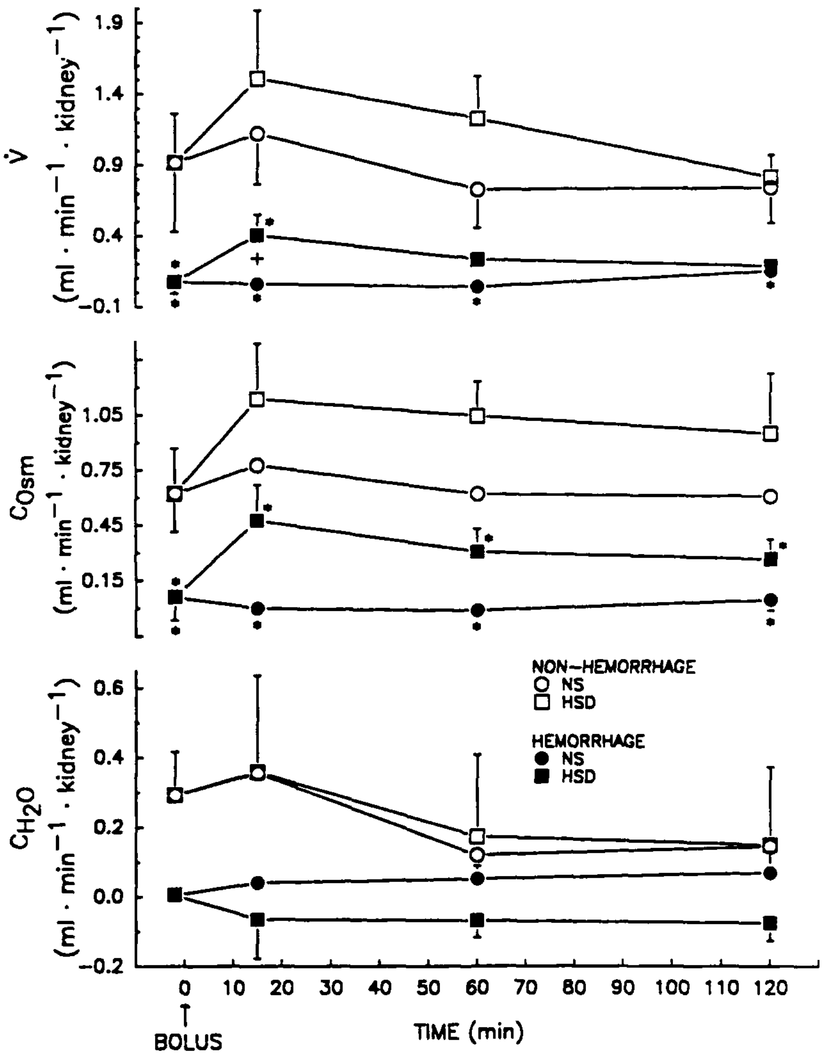


Figure 3: Urine flow rate (V), osmolal clearance (C_{Osm}), and free-water clearance (C_{H2O}) in response to a 4 ml/kg bolus of normal saline (NS) or hypertonic saline/dextran (HSD).

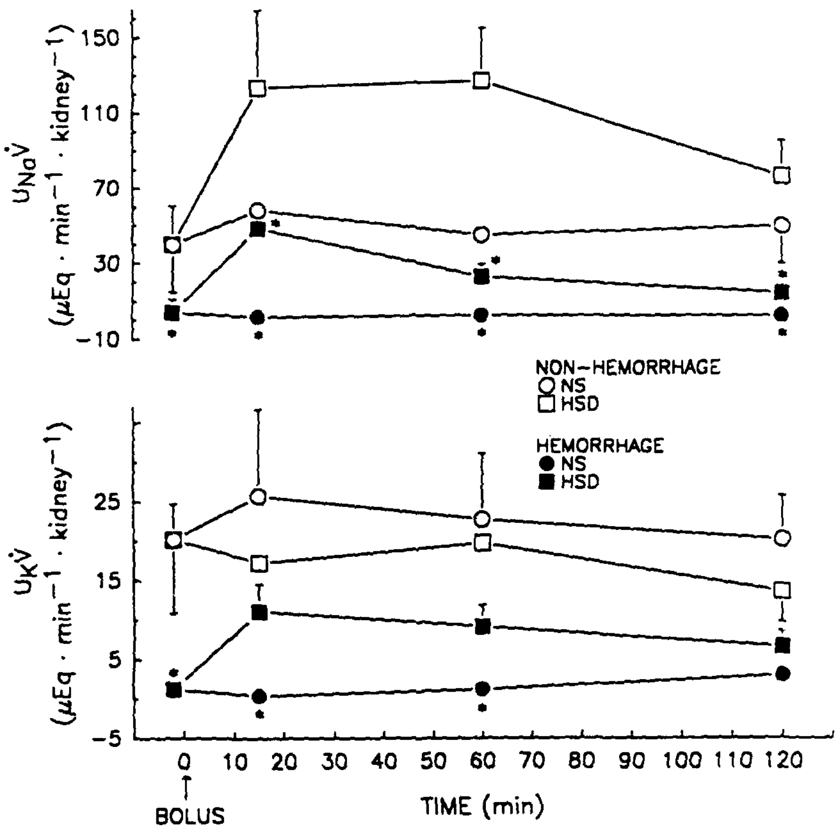


Figure 4: Sodium excretion rate ($U_{Na}V$) and potassium excretion rate (U_KV) in response to a 4 ml/kg bolus of normal saline (NS) or hypertonic saline/dextran (HSD).

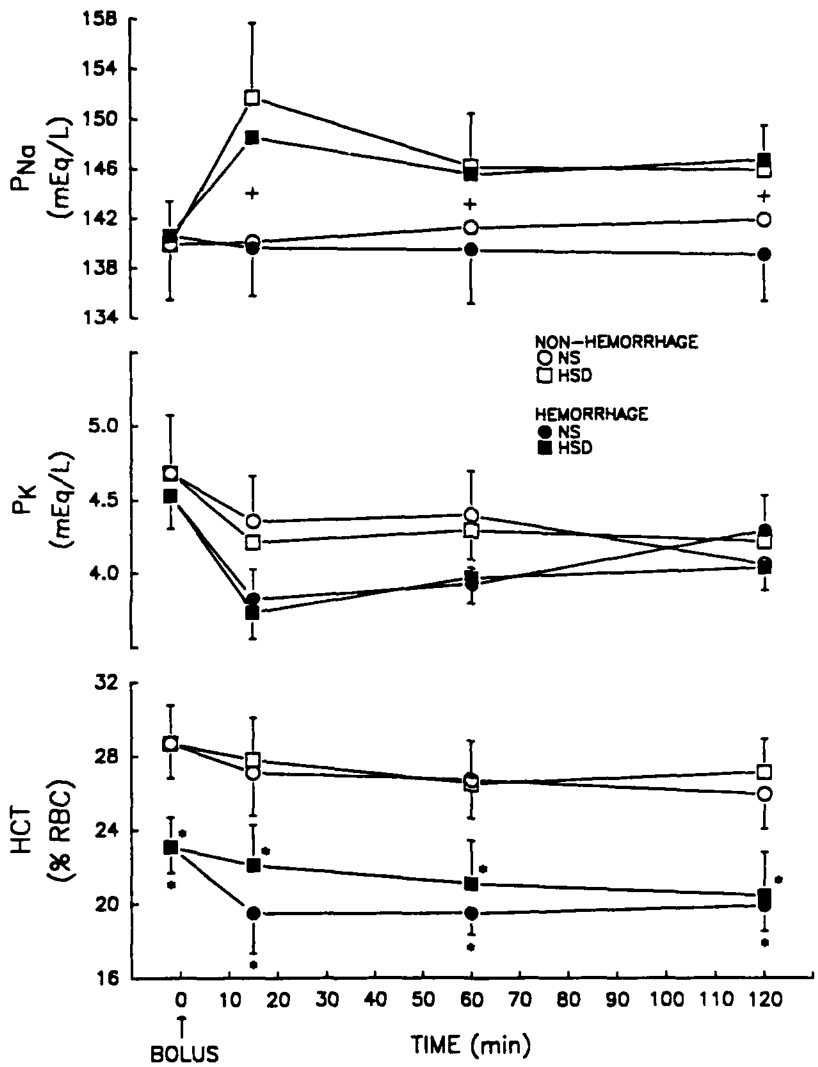


Figure 5: Plasma sodium concentration (P_{Na}), plasma potassium concentration (P_K), and hematocrit in response to a 4 ml/kg bolus of normal saline (NS) or hypertonic saline/dextran (HSD).

OFFICIAL DISTRIBUTION LIST

Commander
US Army Medical Research
& Development Command
ATTN: SGRD-RMS/Mrs. Madigan
Fort Detrick, MD 21701-5012

Defense Technical Information Center
ATTN: DTIC/DDAB (2 copies)
Cameron Station
Alexandria, VA 22304-6145

Office of Under Secretary of Defense
Research and Engineering
ATTN: R&AT (E&LS), Room 3D129
The Pentagon
Washington, DC 20301-3080

DASG-AAFJML
Army/Air Force Joint Medical Library
Offices of the Surgeons General
5109 Leesburg Pike, Room 670
Falls Church, VA 22041-3258

HQ DA (DASG-ZXA)
WASH DC 20310-2300

Commandant
Academy of Health Sciences
US Army
ATTN: HSHA-CDM
Fort Sam Houston, TX 78234-6100

Uniformed Services University of
Health Sciences
Office of Grants Management
4301 Jones Bridge Road
Bethesda, MD 20814-4799

US Army Research Office
ATTN: Chemical and Biological
Sciences Division
PO Box 12211
Research Triangle Park, NC 27709-2211

Director
ATTN: SGRD-UWZ-L
Walter Reed Army Institute of Research
Washington, DC. 20307-5100

Commander
US Army Medical Research Institute
of Infectious Diseases
ATTN: SGRD-ULZ-A
Fort Detrick, MD 21701-5011

Commander
US Army Medical Bioengineering Research and
Development Laboratory
ATTN: SGRD-UBG-M
Fort Detrick, Bldg 568
Frederick, MD 21701-5010

Commander
US Army Medical Bioengineering
Research & Development Laboratory
ATTN: Library
Fort Detrick, Bldg 568
Frederick, MD 21701-5010

Commander
US Army Research Institute
of Environmental Medicine
ATTN: SGRD-UE-RSA
Kansas Street
Natick, MA 01760-5007

Commander
US Army Research Institute of
Surgical Research
Fort Sam Houston, TX 78234-6200

Commander
US Army Research Institute of
Chemical Defense
ATTN: SGRD-UV-AJ
Aberdeen Proving Ground, MD 21010-5425

Commander
US Army Aeromedical Research
Laboratory
Fort Rucker, AL 36362-5000

AIR FORCE Office of Scientific
Research (NL)
Building 410, Room A217
Bolling Air Force Base, DC 20332-6448

USAF School of Aerospace Medicine
Document Section
USAFSAM/TSKD
Brooks Air Force Base, TX 78235-5301

Head, Biological Sciences Division
OFFICE OF NAVAL RESEARCH
800 North Quincy Street
Arlington, VA 22217-5000

Commander
Naval Medical Command-02
Department of the Navy
Washington, DC 20372-5120